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Patty Wilson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Continued Prosecution Application

Under 37 C.F.R. § 1.53(d) Based On:

Application of: LeCluyse, Edward L., et al. Group Art Unit: 1651

Serial No.: 09/527,352 Examiner: Afremova, V.

Filed: March 17, 2000 Docket No.: 421/17/2

For: METHOD OF SCREENING CANDIDATE COMPOUNDS FOR SUSCEPTIBILITY TO BILIARY EXCRETION

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DECLARATION PURSUANT TO 37 C.F.R. §§1.131-1.132

Commissioner of Patents
Washington, D.C. 20231

Sir:

1. I, Kim L.R. Brouwer, am a co-inventor of the invention disclosed and claimed in the subject above captioned U.S. Patent Application Serial No. 09/527,352.

2. A true and accurate copy of my *curriculum vitae*, which evidences my expertise and credentials, is attached herewith and labeled **Exhibit A**.

3. I have had an opportunity to review pending claims 67-200 in the above-referenced U.S. patent application.

4. I have also reviewed the following document: Liu et al., "Biliary Excretion in Sandwich-Cultured (SC) Hepatocytes: A Novel *In Vitro* Model System for Investigating Biliary Excretion," *Pharm. Sci.* 1:S-119 (1998) (Abstract – herein after referred to as Liu et al. [CC]).

5. The invention embodied in claims 105-118 of the subject U.S. patent application was invented prior to the November 16, 1998 publication date of Liu et al. [CC].

6. Attached hereto as **Exhibit B** is a true and accurate copy of a thesis draft prepared by my co-inventor Xingrong Liu while at the University of North Carolina at Chapel Hill. Dr. Liu's dissertation was defended on June 29, 1998. The draft dissertation was provided to the graduate committee at the University of North Carolina at Chapel Hill two weeks prior to this defense date. **Exhibit B** describes the invention embodied in claims 105-118 and predates the November 16, 1998 publication date of Liu et al. [CC]. Please note that the biliary clearance value was defined on page 149, and was discussed throughout Chapter 5, with the greatest detail provided on page 157.

7. I have also reviewed the following documents: LeCluyse et al. (1994) *Am. J. Physiol.* 266:C1764-C1774; Liu et al. (1997) *Pharm. Res.* 24:S-459; U.S. Patent No. 5,602,026 to Dunn et al.; Liu et al. (1996) *Pharm. Res. Init.* 13:S-393 (8003); and Poole et al. (1990) *Archives of Toxicology* 64:474-481 (hereinafter referred to respectively as: LeCluyse et al. [U]; Liu et al. [EE]; Liu et al. [DD]; Poole et al. [V]; and Dunn et al. [A]).

8. The LeCluyse et al. [U] journal article does not teach the quantitation of the excretion of a compound. The LeCluyse et al. [U] is merely concerned with showing a method of culturing hepatocytes to form canalicular networks so as to attempt to provide a representative model to study hepatic morphology and physiology.

9. Dunn et al. [A] does not teach any evaluation of biliary excretion. Liu et al. [EE], Poole et al. [V], and Liu et al. [DD] measure biliary excretion in terms of a biliary excretion index, a percentage of radiolabeled hormone accumulation, and K_m and V_{max}, respectively.

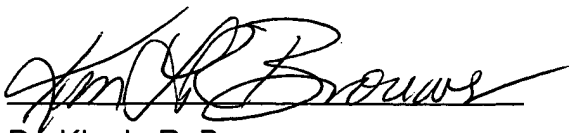
10. LeCluyse et al. [U], Liu et al. [EE], Poole et al. [V], and Liu et al. [DD] do not determine a biliary clearance value, and the biliary clearance value recited in claim 105 is clearly distinct from the approaches described in each of these documents. Biliary clearance is a function of intrinsic biliary clearance and the hepatic plasma flow rate. Compound cleared from blood or plasma into bile involves two processes: uptake across the sinusoidal membrane into the hepatocyte, and excretion across the canalicular membrane into bile. Biliary clearance represents the

volume of blood or plasma completely cleared of substrate that is excreted into bile per unit time, and will be determined by the rate-limiting step in the sequential processes (either uptake or excretion). In contrast, the biliary excretion index determines the fraction of accumulated substrate that appears in bile; thus this calculation only considers transport across the canalicular membrane. To further demonstrate the distinct nature of these calculations, consider the situation where substrate uptake is altered. In this case, if uptake is rate-limiting, the biliary clearance would be altered, but no change in the biliary excretion index would be observed.

11. A true and accurate plot showing a linear correlation of the *in vitro* biliary clearance value to *in vivo* biliary clearance is attached as **Exhibit C**. This plot was prepared using an experimental approach corresponding to that employed to prepare Figure 6B of the subject U.S. Patent Application Serial No. 09/527,352 as filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,



Dr. Kim L. R. Brouwer

May 27, 2003

Date

Enclosures: Exhibits A-C